Definition, measurement, clinical correlates and underlying neurobiology of psychological pain and its relation to suicidal behavior.

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1. Abstract

Psychological pain is a concept, that describes pain in the mind, also know as *psyache*. It is a phenomenon closely related to suicidal acts (Shneidman, 1996; Baumeister, 1990, Troister and Holden 2010). Psycyhological pain is a relatively new concept and not yet that well known, atleast among general practicioners. For example in the USA 5,6% of the general population and 53% of the patients with severe mental illness are thought to suffer from psychological pain (American Psychiatric Association, 2003).

Depression and hopelessness are perhaps the most well known factors in the development of suicidal ideation, atleast for people not familiar with the research literature of this field. However Troister and Holden (Troister and Holden, 2012) compared the effects of psychological pain, depression and hopelessness. The results were that out of depression, hopelessness and psychological pain psychological pain is the only variable that contributes significantly to a change in suicidal ideation. In this study the contributions of depression and hopelessness were reduced to statistically nonsignificant levels. Furthermore psycological pain has been identified as a high risk factor for suicide with a greater predictive power than depression (Olié et al., 2010; Pereira et al., 2010; Troister and Holden, 2010; Li et al., 2014; Troister et al., 2015).

Neuroimaging can be used in psychiatric diagnostics and also in psychiatric research. In diagnostics neuroimaging can be used to for differentiate between psychiatric and somatic causes of a psychosis, as psychosis can arise from a psychiatric disorder or from for example a brain tumor.

Neuroimaging can be used for example in the field of pain research. There is overlap between neural networks of physical and psychological pain, but it seems like these different types of pain have some unique brain areas as well (Meerwijk et al., 2013). In addition to neuroimaging one of the ways of measuring psychological pain is through questionnaires, of which there are several.

Perhaps because of these overlapping neural networks of pain some of the medication used to treat physical pain seems to have a positive effect on suicidal population suffering from psychological pain. It seems like the dose needed to treat psychological pain is a lot smaller than a dose needed to treat equivalent physical pain (Yovell et al., 2016).

2. What is psychological pain?

Psychological pain is an interesting phenominon as it is hard to comprehensively measure objectively, it is experienced subjectively and as a result has proven to be difficult to define. In the research literature psychache, mental pain, psychic pain, psychological pain and internal perturbation are terms that have been used to refer to the same thing – referred in this text as psychological pain.

Psychologial pain has been shown to be quite common in the general population, and it is strongly represented in the group of patients with severe mental illness. In the United States it is estimated that 5,6% of the general U.S. population suffer from psychological pain, while the number is 53% for the patients with severe mental illnesses. (American Psychiatric Association, 2003).

One of the least desired outcomes of severe psychological pain seems to be the act of suicide. It has been shown that psychological pain is more strongly correlated with the act of suicide, than the perhaps more well known affects of depression or hopelessness (Troister and Holden, 2010). Research has shown that psychological pain is one of the most important factors in attemptent suicides (Shneidman, 1996; Baumeister, 1990, Troister and Holden 2010). Therefore it is

reasonable to argue that by better understanding psychological pain we might be able to reduce both the rate of suicide and as an indirect result the amount individual suffering.

2.1 Defining psychologial pain

Defining psychological pain has been a true challenge for the science community. Many attempts have been made, but a comprehensive, generally accepted definition is yet to be found. In this chapter I review the most important definitions and models and try to find common themes between these different views.

It is hard to write a scientific article about psychological pain without mentioning Shneidman. Shneidman is well known for his work on psychological pain and the creation of the term *"Psychache"*. According to Shneidman mental pain wells from a thwarted essential need, which when unsatisfied produces a wild range of negative emotions. These negative emotions are then trasformed to a generalized experince of psychache. (Shneidman, 1980; Shneidman 1993; Shneidman 1996). According to Shneidman psychological pain is at the core of the suicidal process (Shneidman, 1998). Shneidman proposed that psychological pain is a necessary condition for a suicide to occur. In his model other conditions, such as depression, are related to suicidal behavior only through psyache (Shneidman, 1993). The theory that a high level of psychological pain is correlated with suicidality has been later supported by many other independet researchers.

Frankl was a holocaust survivor from Auschwitz, Theresienstadt, Kaufering and Türkheim. He has based a lot of his theories on his experiences as a prisoner of war. Frankl believed mental pain and suffering to well from the loss of meaning in life. This meaning of life could be found again through values that provide meaning to life. In Frankls model mental pain ends, when a meaning for life is found again. (Frankl, 1963). Frankl wrote the book, *"Man's Search for Meaning"* before Shneidman created his theory of psyache, but I believe they both write about the same phenomenon.

Baumeisters is mostly known for his theory of suicide but he is also cited in many articles about psychological pain. Baumeister refers to mental pain indirectly in his theory of suicide. Baumeister views suicide as escape from the self. In his model of suicide mental pain is seen as a state of high self-awareness of inadequacy. According to Baumeister mental pain is felt when the ideal self and it's aspirations are far from the actual self and it's inadequacy. Following this rift between the ideal self and the actual self self-disappointment occurs. In Baumeisters model the core emotion of mental pain is self-disappointment and the suicide is the tool used to avoid this emotion. (Baumeister, 1990).

Bolger analyzed written material from people who had suffered traumatizing experiences, focusing on emotional pain. Bolger defines mental pain as *"brokenness of the self"*, a state that involves experience of being wounded, loss of self, disconnection and, a similiarity with Baumeisters model - awareness of the more negative attributes of one self. (Bolger, 1999).

Mee and colleagues define psychological pain by seperating psychological pain from physical pain - physical pain is usually localised and needs a physical stimulus to be felt, while psychological pain does not. Mee and all wrote about psychological pain in the following way*: "a diffuse subjective experience… diffrentiated from physical pain which is often localized and associated with noxious physical stimuli.".* (Mee et al., 2006).

Some researchers see possibilites to group psychological pain into different categories by quality of the psychological pain and by the intensity of the psychological pain. *"It is proposed that psychological pain may operate on a continuum of intensity from mild to severe or may have distnct subtypes, which are qualitatively different (e.g., the "unbearable" psychological pain in a subgroup of mood disorder patients versus pain associated with a noxious psychological stimulus, such as the death of a child)"* (Mee et al., 2006).

In 2011 Meerwijk and Weiss analysed the literature of psychological pain and defined it as follows: *"a lasting, unsustainable, and unpleasant feeling resulting from negative appraisal of an inability or deficiency of the self"* (Meerwijk and Weiss, 2011). Meerwijk and Weiss also discuss the abilities of the construct of psychological pain by taking into account the temporal domain of psychological pain. Psychological pain is something that takes time to resolve and pass. Psychological pain isn't felt for just a minute or two, it is something that lasts for hours, days weeks or even longer. It is common for the pain to vary in intensity in this period. (Meerwijk and Weiss, 2013).

Li proposes a three-dimensional psychological pain model, wich has a lot of similiarities with the way Schneidman and Baumeister see psychological pain. The first dimension is the arousal of the pain from past memories and experiences, the second dimension is the subjective and bodily symptoms related to the psychological pain and the third dimension is pain avoidance, often with the tendency for suicidal acts. (Li et al., 2014). I believe this to be one of the more completionist views on psychological pain.

Rizvi uses the following words to define psychological pain: *"Psychache refers to the 'hurt, anguish, soreness, aching, psychological pain in the psyche, the mind. It is intrinsically psychological - the pain of excessively felt shame, or guilt, or humiliation, or loneliness, or fear, or angst, or dread of growing old or of dying badly…"*(Rizvi et al., 2017).

According to Jollant *"Psychological pain lies at the heart of the human social experience. It is a natural state in response to particular events, notably those related to loss, grief, failure, shame or guilt."* (Jollant et al., 2018).

Common themes in these definitions of psychache are negative life events leading to psychache, psychache often exisiting alongside hopelessness and depression, the feeling of psychache being far worse than previously felt physical pain and correlation of unbearable levels of psychache with suicidal action. I believe most of these theories or definitions of psychological pain are different views of the same phenomenon. In table 1. I have described the core idea from different reseachers, to make comparison of these ideas easier. Needless to say a lot can be lost in shortening whole theories and definitions into just a few words.

Name*	What causes psychological pain	Year
Frankl	Loss of meaning in life	1963
Shneidman	Thwarted essential need	1980
Baumeister	Self-awareness of inadequacy	1990
Bolger	Brokenness of the self	1999
Meerwijk and Weiss	Negative appraisal of an inability or deficiency of the self	2011
Li et al.	Past memories and experiences	2014
Rizvi et al.	Shame, guilt, humiliation, loneliness, fear, angst, dread of growing old..	2017
Jollant et al.	Events, like loss, grief, failure, shame or guilt	2018

Table 1. Comparison of the theories of psyachem

**Some of the authors discussed in chapter 2.1 are not included in this list. For example Mee focuses on seperating psychological pain from physical pain*

2.2 Distinguishing nociception, different forms of pain and suffering

Physical pain is a different entity from psychological pain. According to Mee et al., the difference is that psychological pain is more of a diffuse subjective feeling, while physical pain can often be localized and is usually associated with a physical stimulus. For the purpose of pain reseach there are different methods to induce a pain signal in the human body. These methods include exposure to

noxious stimuli like heat, cold water baths, laser pulses to the skin, electrical muscular pain and subcutaneous injections of different substances like ethanol or capsaicin (Mee et al., 2006). At the time of writing any comparable method of inducing psychological pain stimulus for a research subject has not been found.

2.2.1 Nociception and physical pain

One of the most used ways to define pain is the definition used by The International Association for the Study of Pain*: "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"* (International Association for the Study of Pain, 1979). Pain treshold is concept, that can be used to differentiate what counts as pain. Pain treshold is defined as the lowest level of stimulus itensity, that is perceived as painful by the individual. Pain tolerance is defined as the greatest duration or itensity of painful stimuli, that the individual is able to withstand. One can think of pain treshold as the minimum amount of pain, as opposed to maximum amount of pain called pain tolerance.

The feeling of pain begins with a stimuli, like a pinprick, that causes the nociceptors to fire which in turn leads to nociception. Nociception (from the Latin word *nocere*, to injure) is signaled throught the peripheral nerve fibres towards the central nervous system, wich finally leads to the brain. In the brain the threat is assessed and protective responses are coordinated.

Nociception is the result of a tissue damage. It is a peripheral process ending in the dorsal horn of the spinal cord, the collection of signals within the central nervous system that is triggered by the injury. Nociception can be followed by pain, which can in turn be followed by suffering, for example if the pain becomes chronic.

Pain is a stimulus that begins in the dorsal horn and ends in the central nervous system. Usually nociception is needed for the generation of pain, but if the nervous system is damaged, pain can be felt without external stimulus. There are also some instances where nociception does not lead into pain, for example general anesthesia.

In healthty subjects the noxious stimulus activates the brain areas of prefrontal cortex, anteriror cingulate, insula, thalamus, cerebellum, parietal and somatosensory cortices, while chronic pain patients show less consistent activation in the prefrontal cortex and the anterior cingulate Anticipation of pain actiates many of these same areas, the components of the nociceptive pathway. In the anticipation of pain the areas of prefrontal cortex, insula, anterior cingulate, somatosensory cortices, thalamus, cerebellum, amygdala and parietal regions are activated. (Mee et al., 2006).

2.2.2 Suffering

Mirriam-Webster, the dictionary, defines suffering as a *"..state of being in great trouble."* and that *"Suffering implies conscious endurance of pain or distress."*.

Suffering is a negative affect that is connected to pain, but can excist independetly of any pain. Suffering can also be the end result of pain. For example losing a foot can cause suffering, even when the pain is being managed by medicine or has already passed. As Loeser eloquently put it *"suffering can be the result of pain, or it can be engendered by many other states, such as fear, anxiety, depression, hunger, fatigue, or loss of loved objects. Suffering exists only in the mind and the events that lead to suffering will differ from one patient to another. "* (Loeser, 2000). Loeser defines suffering as a *"negative affective response generated in the brain in response to pain, fear, anxiety, depression and other states."* (Loeser, 2000).

Frankls view of suffering is that in it's core suffering is based on existential frustration. He saw suffering being born from the loss of meaning in life, that resulted in a feeling of emptiness. In

Frankls theory suffering could be stopped by finding meaning to life. Frankl didn't see this suffering as something intrisictly pathological or as a mental disease. (Frankl, 1963).

According to Cassell suffering is closely related to threats and fears and concerns about what the future holds. Suffering varies in intensity and in duration, depending on the particular person experiencing the sufffering. For example the loss of a foot is painfull and tragic to anyone, but the amount of suffering it causes is different for a bed-ridden patient in palliative care than it is for a professional athlete. Because of the myriad of factors making up the personality of each indvidual human the amount of suffering from the aforementioned foot amputation differs from athlete to athlete – from person to person. Cassell defines suffering in the following way: *"Suffering has been defined as a specific state of distress that occurs when the intactness or integrity of the person is threatened or disrupted. It lasts until the threat is gone or integrity is restored."* (Cassell, 1999).

In my understanding a definitive and all encompassing definition for suffering has not been made. As shown above different authors all write about suffering and even though there are a lot of similiriarities, such as seeing suffering as a response to a negative affect of the mind, there are also differences. For example Frankls view of suffering as a loss of meaning in life versus Loesers focus on negative affects. Then again Casall and Frankl seem to be writing about the same phenomenon – it is possible to imagine that loss of feeling in life results in disturbed intactness of a person.

2.2.3 Temporal aspects of pain

In addition to being able to divide pain into physical and psychological components, pain can also be classified into transient, acute or chronic pain. Transient pain is defined as pain that *"ceases as soon as the stimulus is removed"* (Loeser, 2000). Acute pain is defined to be caused by an injury to the body tissues and as the result of nociceptive transducers activating. Chronic pain is pain that resultus usually from an injury, but may also be the result of a myriad of factors, that are different from the primary cause of pain. The cause of chornic pain might be for example damaged nervous system, that is incapable of healing. The difference between acute and chronic pain is the ability of the body to heal the injury and normalize the working of the nervous system producing the pain signal. (Loeser, 2000).

This temporal aspect of pain can also be shown with brain imaging. Acute physical pain shows as the activation of the prefrontal cortex, anterior cingulate, insula, thalamus, cerebellum, parietal and somatosensory cortices, while in chronic pain the activation is lesser in the prefrontal cortex and anterior cingulate.

According to Meerwijk and Weiss, psychological pain tends to be on the chronic side, and it is uncommon to feel psychological pain for just a minute or two. The nature of psychological pain is that the intensity of psychological pain tends to vary with time. (Meerwijk and Weiss, 2013). The temporal aspect of physical pain is on the transient or acute side. For example hitting your finger with a hammer can cause transient or acute pain depending on the force of the blow. Physical pain can also become chronic for example in a case of nerve injury. If physical pain becomes chronic, it also has a tendency of varying with time. A common theme in chronic pain is that it is dependent on the life situations – in a time of high stress the intensity of the pain tends to increase.

2.2.4 Differentiating psychological pain from suffering

In the field of psychological pain one of the important developments has been the developement of the language used to specify different emotions. Psychological pain and psychic suffering could also benefit from a generally accepted and clear definitions. I would reckon that psychological pain and suffering are closely related, as they have common themes such as tendency to become chronic and

being highly subjective and as such hard to quantify. One such definition attempt was made by Fleming (Fleming 2006) and it is based on the psychoanalytic theory.

In 2006 Fleming proposed to use 'mental pain' and 'psychic suffering' to name distinct emotional experiences of the patient. Fleming bases her distinction in the work of Bion (Bion, 1970, p. 19), especially in the following statement: *''the patients come for treatment, of whom I wish to formulate theories, experience pain but not suffering ...the intensity of the patient's pain contributes to his fear of suffering pain ... pain is inflicted or accepted but is not suffered, except in the view of the analyst or other observer''* (Fleming, 2006).

Fleming wrote *"Mental pain refers to a pain that the patient reports as being impossible to describe in words, and lacking any associations, whereas psychic suffering can be both named and described by the patient."* (Fleming, 2006). According to Fleming, mental pain is derived from traumatic experiences, that are not suitable for mental elaboration.. Because the traumatic experiences have not been elaborated, they cannot be constructed into the higher levels of mental complexity, like symbolization – and that is why they are expressed as mental pain. Fleming defines psychic suffering to be the result of a negative experience that has been tolerated by the mind. In Flemings model there is a personal treshold for emotional pain for each patient. On the other side of this treshold there is mental pain and on the other psychic suffering. (Fleming, 2006).

This definition of mental pain closely resembles the definitions used to describe psychological pain. It could be the authors are discussing the same phenomenon with different terms. The path from mental pain to psychic suffering proposed by Fleming (Fleming, 2006) closely resembles Loesers (Loeser, 2000) idea that suffering can be the end result of pain.

2.2.5 Differentiating psychologial pain from physical pain

Differences between psychological and physical pain are numerous. From the point of locating the pain, physical pain is often localized and most often results from a noxious physical stimulus (Mee et al., 2006) while psychological pain generally doesn't have a specific location. Temporal differences are shown in the chapter 2.2.3, generally physical pain can be trasient, acute or chronic and usually leans on the shorter time scale, while psychological pain affects usually a longer time period. Both forms of pain cause detectable changes in brain tissue. Unique aspects of physical pain seem to be the activation of somatosensory cortices (Mee et al., 2016, Meerwijk et al., 2013) while the brain areas involved in psychological pain are located in the medial subcortical area. (Meerwijk et al., 2013). This is written in more depth in the chapter 4.5.3.

One way to differentiate psychological pain from physical pain is other symptoms commonly associated with these different forms of pain. One way to analyze the differences of psychological and physical pain is to consider the negative affects they often associate with. Psychological pain is mainly correlated with depression and hopelessness, while physical pain is mostly correlated with anxiety (Jollant et al., 2017).

There have been some studies (Osmond et al., 1984), with a low number of patients, that suggest that psychological pain is generally worse than physical pain. In Osmonds study 30 patients with depressive symptoms and a history of life threatening physical illness or trauma were chosen. Physical illnesses and injuries included for this study were for example cancer, heart attacks and multiple surgeries. The result was that 28 of 30 patients reported that their psychological pain, accosiated with depression, was worse than any phyiscal pain they had experienced from their injuries and illnesses. (Osmond et al., 1984).

3. How can we measure psychological pain with questionnaires?

One of the ways to measure psychiatric symptoms is with questionnaires. For example other negative affects, like depression and anxiety, have clinically usable scales to asses the level of depression or anxiety of a patient and these can be used to asses the need for a psychiatric intervention or medication. Psychological pain has also several different questionnaires, of which the most well known are shown in this chapter.

3.1. What is Cronbach alpha?

Cronbach alpha, also known as coefficient alpha, is a coefficient that can be used to internally value the correlation of questions in a specific questionnaire. This is done in order to streamline the questionnaire and to remove or modify questions, that are not in line with the intended purpose of the questionnaire. In some of the scales discussed below the creators of the scale in question have also measured a Cronbach alpha coefficent to better assess the functionality of the scale. Generally values above 0,8 are consifered to be adequate, while values below 0,6 are considered to be weak.

3.2 Different scales of measurement

The number of different scales used to measure psychological pain are in the low tens. Some of the scales developed for this purpose are quick, self-fillable tests, that can be used clinically in just a few minutes, while others require trained personel to administer and interpret. As of today there has not been a single scale that would be clearly superior as the different scales each have their strengths and weaknesses.

3.2.1 PPAS

The first scale to be made for the measuring of psychological pain is Shneidmans Psychological Pain Assessment Scale (PPAS). PPAS, requires a trained operator firstly to administer the test and secondly to interpret the results. PPAS has a series of five pictures with scales from 1 to 9, on wich the test taker rates the psychological pain of the main character in that picture. The test taker is also asked to rate his or her worst mental pain on a nine point scale.

After the scales the test taker is asked to checkmark from a list of 22 negative emotions three emotions that were present when he or she was in pain. Attempted suicide is also asked, as well as the method of the attempted suicide and the severity of most serious suicide attempt. In the end there is a written essay component with the text *“Please describe beow how your worst psychological pain felt, what the circumstances were, and how it worked out. Thank you.”*. (Shneidman 1999).

PPAS is reported to have a modest validity (Pompili et al., 2008) and is pretty cumbersome to use, since it reguires a trained operator to administer and to interpret the results.

3.2.2 PAS

The Psychache Scale, PAS, was developed and validated in a group of undergraduate students (Holden et al., 2001). PAS is the most widely used of the psyache scales. It has 13 items with a 5-point Likert scale. The PAS can differentiate between suicide attempters and nonattempters (Holden et al., 2001), has a high realibility and validity (Mills et al., 2005; Flamenbaum and Holden, 2007; Troister and Holden, 2010, 2012; Patterson and Holden, 2012), with cronbach alpha coefficients of .92 and .95 reported in university and offender populations (Holden et al.; Mills et al., 2005). The criticism for the scale has been that even though it is good in measuring the frequency of psychological pain it doesn’t measure the intensity of psychological pain (Mee et al., 2011).

3.2.3 OMMP

Orbach and Mikulincer Mental Pain Scale (OMMP) was created as a multi step process by Orbach and Mikulincer in 2002. The first step taken to create the OMMP, Orbach and Mikulincer created a pilot study with a narrative approach. The group interviewed by the authors consisted of inpatients and healthy individuals and they were asked a group of questions related to mental pain, this was the basis for the first version of the OMMP scale.

OMMP has nine factors that are: irreversibility, loss of control, narcissist wounds, emotional flooding, freezing, self-estrangement, confusion, social distancing and emptiness. OMMP has 40 questions and is constructed as a 5 step Likert scale. The Cronbach alpha coefficients for the nine factors were considered to be acceptable, witch implies adequate internal consistency (Orbach et al., 2003). The reliability of OMMP was tested as a test-retest examniation, with a 3-week interval and a new sample of people. The test-retest coefficents for the nine scales were between .79 and .94, proving the scale to be reliable (Orbach et al., 2003). OMMP is able to distinquish suicide attempters from nonattempters (Gvion et al.,2014; Levi et al.,).

3.2.4 PPP-VAS

PPP-VAS stands for Physical and Psychological Pain Visual Analog Scale. The first publication of this scale was by Olie et al in 2010 and it was later validated by Jollant et al in 2019. PPP-VAS measures pain in six dimensions: current, mean and worst physical pain in 15 days followed by current, mean and worst psychological pain in 15 days. These dimensions are marked as horizontal rectangles, with extremities labeled as “no pain” on the left and “maximal pain” on the right. Another version of this scale has numbers from 0 to 10 instead of the rectangles and instructions to circle the appropriate number for each of the six dimensions. PPP-VAS can be filled in less than one minute, wich makes it a powerful tool for the clinical practicioner looking to gain insight on his patients psychological pain status. (Jollant et al., 2019).

3.2.5 MBPPAS

The Mee-Bunney Psychological Pain Assessment Scale (MBPPAS) was developed by Mee and Bunney in 2011 for quick and reliable assessment of psychological pain and risk of suicidality in clinical patients. MBPPAS is a five level Likert scale with ten items and it is characterized as “..a brief 5min self-report scale..” (Mee et al., 2011). The scale is self-rating and measures intensity and frequency of psychological pain. MBPPAS assesses frequency and intensity of current psychologial pain and psychological pain experienced within three months. (Mee et al., 2011).

The validity of MBPPAS was demonstrated using Pearson correlation cofficients between MBPPAS and hand picked tests used in psychiatry to measure specific negative affects. The affects and tests used in demonstrating the validity of MBPPAS are: depression (Becks Depression Inventory, BDI (Beck et al., 1961)), hopelessness (Becks Hopelessness Scale, BHS (Beck et al., 1974)), physical pain (Brief Pain Inventor, BPI (Cleeland and Ryan, 1994)) and suicidality (Suicidal Behavior Questionnaire, SBQ (Linehan and Addis, 1990)). MBPPAS scores were significantly correlated with depression (BDI), suicidality (SBQ), physical pain (BPI) and hopelessness ratings (BHI). The Cronbach alpha was also measured for MBPPAS and all the items had an value of > 0,75. Effect on the Cronbach alpha was also tested by removing individual items, wich resulted in no signifficant effect. (Mee et al., 2011).

Scale	Number of questions	Likert scale	Cronbach alpha	Year of publication	Maker	Suitable for general clinical usage
PPAS	31	No	N/A	1999	Schneidman	No, requires a trained professional.
PAS	13	Yes	0.92 - 0.95	2001	Holden et al.	Yes, designed as such.
OMMP	40	Yes	0.78-0.95	2003	Orbach and Mikulincer	No, it is very long.
PPP-VAS	6	No	N/A	2010	Olie et al.	Yes, designed as such.
MBPPAS	10	Yes	0.83-0.94	2011	Mee and Bunney	Yes, designed as such.

Table 2. Comparison of the scales of psyache

4. Psychological pain is closely related to suicidal ideation and suicidal acts

The connection of psychological pain and suicidal acts is well establsihed (Shneidman, 1996; Baumeister, 1990, Troister and Holden 2010). For the purpose of this article suicidal ideation is defined as thoughts of suicide or preparing for the suicide in the level of thought. Suicidal acts are then defined as actions directly relating to the attempted suicide – from collecting the necessary equipment to perform the deed to the actual attempted suicide. For the purpose of this article self harm and self mutilation are grouped into non-suicidal self injury (NSSI). NSSI is further discussed in the chapter 4.1.4.

There are many theories for suicidal actions, most based on the feelings of depression and hopelessness. These theories are further discussed in chater 4.2. Depression is one of the most used predictors of suicidal ideation, but the problem is, that it does not appear to distinguish attempters from those, who only exhibit suicidal ideation (Klonsky and May, 2016). Hopelessness is also used in prospective prediction of suicidal ideation and attempted suicides, but the magnitude of this prediction is similar to a correlation of about 0.2 (Beck et al., 1989).

Psychological pain is superior to previously used predictors of suicidality and suicidal ideation, and has been demonstrated to be able to distinguish more reliably than depression or hoplessness, those who exhibit suicidal ideation from those who attempt suicide (Pereira et al., 2010). In recent years there have been several studies, that have given evidence about the relationship between psychological pain and suicidal ideation – and the concensus seems to be that psychologial pain is more strongly correlated to suicidality than any of the previoisly used affects like depression or hopelessness. Psychological pain is the reason most often reported for suicide (Ducasse et al., 2018).

Psychological pain has been proven to be correlated with suicidality in a variety of populations – ranging from psychiatric care patients to homeless men (Patterson and Holden, 2012) and college undergraduates. Intrestingly psychological pain is correlated with suicidality in several studies, but for example physical pain and pain severity is found to be correlated in some studies (Fishbain 1999), while the results in other studies have been negative (Smith et al., 2004).

Psychological pain has been shown to be a strong predictor of suicidal ideation (Troister and Holden 2010). It has also been shown to be more accurate statistical predictor of suicidality than

either depression or hopelessness (Pereira et al., 2010). Psychological pain has also been shown to connect a variety of different constructs to suicidal behavior, like perfectionism and suicidality (Flamenbaum and Holden 2007). Psychological pain propably cannot explain suicidality completely, it is propable that the reality is something akin to what Mee et al. (Mee et al., 2006) hypotized (Figure 1.).

Based on multiple studies (Olié et al., 2010; Pereira et al., 2010; Troister and Holden, 2010; Li et al., 2014; Troister et al., 2015) psychological pain has a greater predictive power for suicide than depression does. According to Nock et al. (Nock et al., 2010) depression is not needed for a person to be suicidal (Nock et al., 2010). In the light of this evidence figure 1. (Mee et al., 2006) Could be modified to emphasize the role of psychological pain.

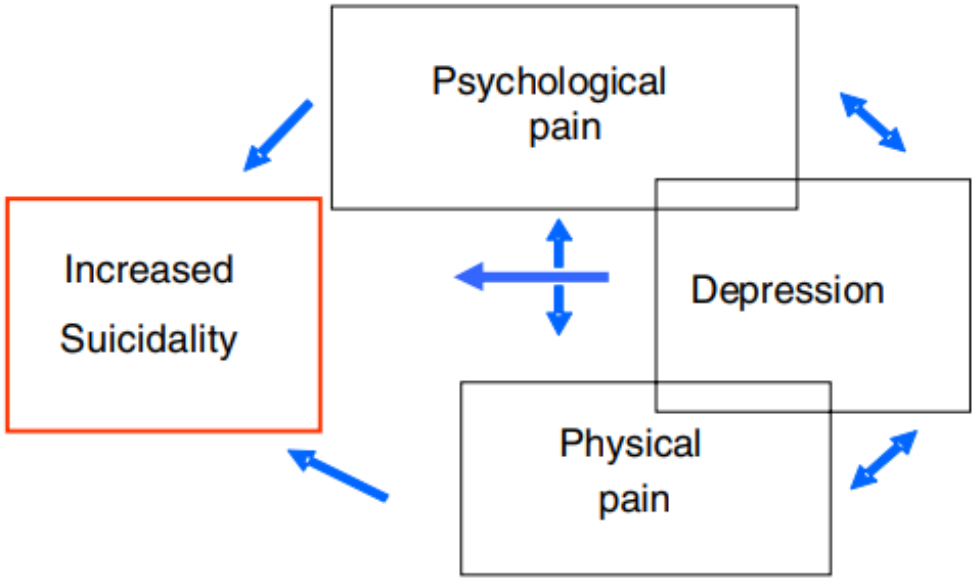

Figure 1. Hypotized connection of depression, psychological pain and physical pain with increased suicidality. Copied from Mee et al., 2006.

4.1.1 Epidemology of suicide

Suicide as a phenomenon occurs globally estimately 11.4 per 100 000 people per year, though the data used in this estimate is not precise. The problem with the data is that only 35% of WHO member states have comprehensive vital registration within the last five years. The rate of suicide varies between and within countries. This variation can be as high as ten-times between different regions and it is partly explained by economic status and cultural differences. (WHO, 2014). It has been surmised that cultural differences might trump over geographical ones, as the suicide rate of immigrants is closer to the suicide rate of their country of origin rather than their country of residence (Spallek et al., 2014). The lifetime average in the globe for suicidal ideation is 9,2% and the lifetime average for an attempted suicide is 2,7% (Nock et al., 2008).

Research has also been able to find that individuals that report suicidal ideation within the last 12 months are in high risk of an attempted suicide. The 12-month prevalence rates for this group is 15,1% in high-income countries and 20,2% in low-income countries. If there is suicidal planning in addition to suicidal ideation the risk of an attempted suicide rises even higher. (Borges et al., 2010).

4.1.2 Suicidal acts in different populations

Suicidal acts are distributed unequally among the population. The WHO World Mental Health Survey suggest that the average 12-month prevalance of suicidal ideation in high-income countries is 2,0% opposed to the average of low-income countries, that is 2,1%. The prevelance of suicide attempts is 0,3% in the high-income countries and 0,4% in the low-income countries. (Borges et al., 2010).

Suicide attempters can also be grouped further within high-income countries and low-income countries. In high-income countries the most prevalent group are middle-aged and elderly men, even though there has been a trend of rising rate of suicide in young people - suicide is the second highest cause of death in individuals aged 15 to 29 years. (WHO, 2014).

One way to further analyze the groups of suicide is to group individuals based on their sex. Generally women have higher rates of suicidal ideation and suicide attemtps, while men have higher rates of death by suicide the ratio of male to female deaths by suicide varies within different groups and areas. In high-income countries this ratio is 3,5, when low-to-middle-income countries have a ratio of 1,6. Europe and the Americas have a ratio of 3,6 - 4,1 when Asian Pacific countries have a ratio of 0,9 - 1,6. (WHO 2014).

Women exhibit more non-lethal suicidal behavior than men. Non-fatal suicidal behavior is more common in people who are socially disadvantaged, such as those with low income, unemployed and those with low education. Non-fatal suicidal behavior is also increased in young people and unmarried individuals (Nock et al. 2014).

Disadvantaged groups seem to have an increased risk of suicide, atleast in high income countries. Canadian prison population the risk of suicide is six-fold, when comparing to the general population (Mills et al., 2005). As another example of this unequally distributed suicidal behavior is the fact that the suicide rate among homeless people is substantially greater than the general population (Fitzpatrick et al., 2007; Schutt et al., 1994). It has been shown, that 90% of people who have died by suicide have been suffering from a psychatric disorder before their death (Cavenagh et al., 2003).

4.1.3 Theories of psyache can help to explain suicidal actions

Shneidmans theory of psyache is at the roots of the discussion concerning the relationship of suicidal ideation and psychological pain. According to Shneidman depression and hopelessness are related to suicide only throught their association with psychological pain. According to Shneidman psychological pain is also in the core of the suicidal act. In this model suicide occurs, when psychological pain becomes unbearable and the only percieved way to stop the psychological pain is the act of suicide. (Shneidman 1999).

Shneidman's psychache model has been reviewed and it has empirical support. For example DeLisle and Holden (DeLisle and Holden, 2009). explored the relationship of depression, hopelessness and psyache and found that psychache accounted for more variance in depression and hopelessness than either accounted for in psychache. The amount of psychache was also correlated with the risk of suicide, when previous suicide attempts and current suicidal ideation was used to measure the risk of suicide. (DeLisle and Holden, 2009).

Holden et al. (Holden, Mehta et al., 2001) proved that hopelessness doesn't predict suicidal ideation, when psyache is statistically controlled. This is thought to be a strong implication that psychache acts as the link from hopelessness to suicidal ideation. According to Patterson and Holden (Patterson and Holden, 2012) *"..psychache may currently be the best predictor for suicide ideation."* In their reseach of homeless men Patterson and Holden (Patterson and Holden, 2012) found that psychache correlates significantly with suicide ideation, motivation, preparation and attempt history. In the same study psyache had higher correlations, than depression, hopelessness or life

meaning (Patterson and Holden, 2012). Psychological pain has been identified as a high risk factor for suicide with greater predictive power than depression (Olié et al., 2010; Pereira et al., 2010; Troister and Holden, 2010; Li et al., 2014; Troister et al., 2015).

A study about the relationship of psychological pain, depression and hopelessness to suicidal ideation was performed with a group high-risk individuals. The results were that psychological pain was the only variable to contribute a significant, unique explanatory variance to the prediction of change in suicide ideation, over a two year period. In this study controlling for psychological pain statistically reduced the contributions of depression and hopelessness to nonsignificant levels, making a case for Shneidmans theory of other predictors being relevant to suicidal ideation in terms of their association with psychological pain. (Troister and Holden 2012).

According to Baumeister a conclusion that depression causes suicide is problematic, as most depressed people do not attempt suicide and not all suicide attempers are clinically depressed. Also if hopelessness is controlled statistically, depression ceases to be predictive to suicide (Baumeister, 1990). Nock et al. have found similar results. *"Individuals with no depression can show suicidal behavior"* (Nock et al 2010).

4.1.4 Non-suicidal self injury

Suicide is defined as the act of an individual ending their own life. Non-suicidal self injury (NSSI) is strongly correlated with suicidal ideation and behavior (Klonsky et al., 2013), but is a distinct phenomenon from an attempted suicide. NSSI is usually performed by cutting or burning, while self-poisoning is more prevalent for attempted suicides. NSSI is often an attempt to temporarily relieve overwhelming negative emotions and sometimes as an attempt to avoid suicidal urges. The other differences between NSSI and suicidal behaviour include, but are not restricted to, frequency, prevelance and severity.

NSSI is generally more prevalent and frequent phenomenon, since it is often performed dozens or hundreds of times, while suicide is commonly attempted only once or a few times. Attempted suicide is also usually more severe, since NSSI rarely causes medically severe or lethal injuries. (Klonsky et al., 2016).

4.2.Ideation-to-action framework

Variables of suicidal ideation, including but not restricted to, depression and hopelessness, are good predictors of suicidal ideation. Depression and hopelessness are able to predict suicide attempters among suicide ideators only weakly (Klonsky and May 2010, Klonsky and May 2016). In their 2016 meta-analysis Klonsky and May compared the variables of depression and hopelessness with attempters to ideators, with the result of the effect sizes for depression and hopelessness dropping to near zero (Klonsky and May, 2016).

In the ideation-to-action-framework suicidal ideation and the progression from suicide ideation to suicide attempts are treated as individual processes and thus they are considered to have different predictors and explanations. The ideation-to-action-framework has several levels from research design to clinical correlates. Klonsky and May criticize most studies, for comparing attempters to a nonsuicidal group. According to Klonsky and May this should be stopped, since almost all of the suicide attempters have also experienced suicidal ideation. Klonksy and May propose that most studies should compare suicide attemptres to suicide ideators. (Klonsky and May, 2016).

Another aspect of ideation-to-action-framework is the constructive criticizm of earlier theories of suicides emphasizing many different factors, such as Shneidmans theory (Shneidman 1985, 1993) focusing on psyache, and Baumeisters theory (Baumeister 1990) of escape from self-

cognition, that is too much to handle. Klonsky and May praise these theories for advancing the field, but also see a common limitation in these theories: the lack of explanation for development from suicidal ideation to actual acts of suicide. (Klonsky and May, 2016).

Outside of theory and research the ideation-to-action-framework can be applied to domains, such as prevention and risk assesment. In prevention for example the ideation-to-action-framework can be used to separate the interventions meant to help with suicidal ideation with the interventions meant to hinder suicidal actions. (Klonsky and May, 2016).

Ideation-to-action framework includes three different theories of suicide. These are interpersonal theory, developed by Joiner in 2005, integrated motivational-volitional theory, developed by O'Connor in 2011 and finally three-step theory, developed by Klonsky and May in 2011. These theories are summarized in table 2 and only three-step theory is discussed further in this paper, as it is the one most closely connected to psyache. Table 3 compares the traditional approach of earlier suicide theories to the approach of ideation-to-action framework.

Theory	Main factors causing suicidal ideation	Main factors causing progression from ideation to attempts
Interpersonal (Joiner 2005)	Perceived burdensomeness and thwarted belongingness	Acquired capability for suicide
Integrated motivational-volitional (O'Connor 2011)	Defeat and entrapment (facilitated by threat-to-self and motivational moderators)	Capability, impulsivity, planning, access to means, imitation, and other volitional moderators
Three-step (Klonsky & May 2015)	Combination of pain and hopelessness, especially when pain exceeds connectedness	Dispositional, acquired, and practical contributors to increased capacity for suicide

Table 3. Ideation-to-action framework. Copied from Klonsky and May 2016

The difference between the (*a*) traditional and (*b*) ideation-to-action approaches to suicide. The traditional approach treats suicide risk as a unitary construct; in contrast, the ideation-to-action framework distinguishes predictors of ideation from predictors of the progression from ideation to behavior[a]

(*a*) Traditional approach	(*b*) Ideation-to-action framework	
Risk factors for suicide	Risk factors for suicidal ideation	Risk factors for suicide attempts
Mental disorders	Mental disorders	Certain mental disorders (e.g., posttraumatic stress disorder)
Depression	Depression	Access to lethal means
Hopelessness	Hopelessness	Knowledge/comfort with lethal means
Impulsivity	Impulsivity (most forms)	Impulsivity (poor premeditation)
Access to lethal means	Nonsuicidal self-injury	Nonsuicidal self-injury
Knowledge/comfort with lethal means	. . .	. . .
Nonsuicidal self-injury	. . .	. . .
. . .	. . .	. . .

[a]This table is meant to be illustrative, as indicated by the ellipses in each column; it is not a comprehensive account of suicide risk factors.

Table 4. Comparison of traditional suicide theories to the ideation-to-action framework. Copied from Klonsky and May 2016.

4.2.1 The three-step theory of suicide

In 2015 Klonsky and May developed the three-step theory of suicide (3ST) (Klonsky and May, 2015) which is meant to improve understanding and prediction of suicide, suicidal behavior and suicide ideation. 3ST has a variety of key concepts, including pain, hopelessness, connectedness and suicide capability. 3ST is illustrated and summarized in figure 1., in which the three steps of the 3ST are clearly divided for claritys sake. The three steps of 3ST are development of suicidal ideation, strong versus moderate ideation and progression from ideation to attempts. (Klonsky and May, 2016).

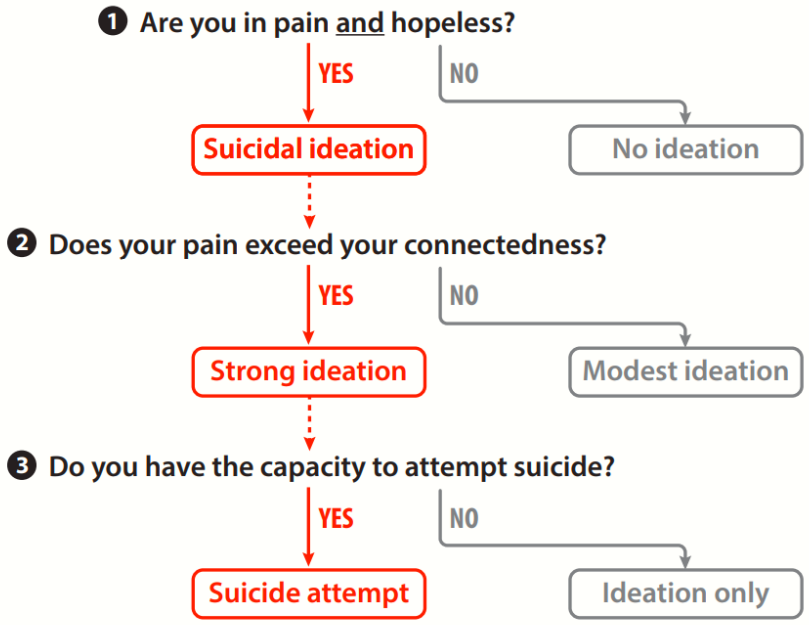

Figure 1

The three-step theory (3ST) of suicide. Key constructs of the 3ST are pain and hopelessness, connectedness, and suicide capacity. Figure adapted from Klonsky & May (2015).

Figure 1 taken from Suicide, Suicide Attempts and Suicidal Ideation by Klonsky and May, 2016.

The first step toward suicidal ideation is thought to begin with pain, which in this instance is typically, but not necessarily, of the psychological or emotional variety. One way to explain the effect of emotional pain on a persons will to live, is a model where human behavior is inspected through reward and punishment. If one's experience of life is filled with pain, the person is question can be thought to be punished for being alive, which in turn can be thought decreases the will to live. In this theory the source of the pain is not important, it can be physical for instance from a burn wound or emotional, such as the pain from social isolation. Also pain alone is not sufficient to cause suicidal ideation. As long as individual has hope that the pain can be diminished and that his situation can improve, generally the individual will strive towards a future without pain rather than consider the path of suicide. Thus pain without hopelessness is not usually enough to push a person into attempting suicide. (Klonsky and May, 2016).

The second step in 3ST is thought to occur when pain exceeds connectedness. When using the term connectedness in this context, it is defined as *"any sense of purpose or meaning, that keeps on invested in living."* (Klonsky and May, 2016). This definition is quite broad and can practically mean for example an actual connection to other people, a project or interest in something – as long as it keeps one invested in living. In 3ST it is thought that as long as the pain experienced by the person conteplating suicide is smaller than the connectedness experienced by this person, the suicidal ideation is considered to be moderate. When the experienced pain becomes greater than the connectedness, ideation becomes strong. Klonsky and May describe moderate suicidal ideation with the following quote *"Sometimes I think I might be better off dead"* (Klonsky and May, 2016) and strong suicidal ideation with *"I would kill myself if I had the chance"* (Klonsky and May, 2016). In 3ST connectedness is thought to be a protective force. It protects against rising suicidal ideation, that is caused by pain and hopelessness. Disturbed connectedness can lead to pain and hopelessness, but pain and hopelessness can exist without disturbed connectedness. The connection between

disturbed connectedness and suicidal ideation is similar – one can have suicidal ideation independent of disturbed connectedness and one can experience distrubed connectedness without it developing to suicidal ideation. (Klonsky and May, 2016).

The second step of 3ST is thought to take place, when ones pain exceeds ones connectedness. One way for this to happen is by the effect of other negative affects, such as depression, personality traits and / or negative life experiences. 3ST acknowledges these phenomenons as contributors to suicidal ideation, but they are not thought to contribute directly, rather they contribute indirectly through their effect on pain, hopelessness and / or connectedness. (Klonsky and May, 2016).

The third step of 3ST describes the conditions that underlie the progression from strong suicidal ideation to a suicide attempt. In the third step the 3ST broadens the theory of suicide by Joiner (Joiner, 2005) which portrays fear of death is a powerful instinct, that has to be overcome. 3ST agrees with this premise, but broadens the ways to overcome this instinct. 3ST proposes variables, that are grouped into three groups and are used to overcome fear of death. These groups are dispositional, acquired and practical group. They are further discussed in the chapter 3.3. (Klonsky and May, 2016).

4.2.2 Capability for suicide

Capability for suicide is a concept by Thomas Joiner in his Interpersonal-Psychological Theory of Suicide(ITPS) (Joiner, 2005). The main idea of ITPS is that pain, injury and death are negative events and humans are biologically and evolutionarily wired to fear them. In order to attempt suicide, one must overcome these fears. Klonsky and May (Klonsky and May, 2016) further expanded the concept of capability for suicide by grouping different contributing factors. The groups proposed were dispositional, acquired and practical contributors

Dispositional group consists of relevant variables each individual is born with. In their 2016 article Klonsky and May give an example based on the work of Young (Young et al. 2012), in which Young states, that people are born with varying degrees of pain sensitivity. It is thought, that a person with lower pain sensitivity has a higher risk of suicide, and based on the second step of 3ST this makes sense. If pain sensitivity is lower, then the experienced pain is higher and thus it is more propable for the pain to be higher than a persons connectedness. Dispositional group is based on the idea, that factors each person is born with affect his propability of an attempt for suicide. Findings made by Smith (Smith et al. 2012) support this claim by suggesting, that the capability of suicide is largely based on genetics (Smith et al. 2012).

Acquired group consits of variables acquired through time. Klonksy and May (Klonsky and May, 2016) have written considerably less from this group, when compared to dispositional and practical groups. The general idea is that experiences associated with negative affects, such as pain, fear, injury and death can lead to habituation to these experiences. And in turn this habitutation can lead to higher capaticty for a suicide attempts. (Klonsky and May, 2016).

The last group important in the third step of 3ST is the practical group. In this group the variables are concrete factors, that affect the attempt of suicide by making it easier. This is a diverse group and there are many kind of practical factors. For example a person that owns a firearm and has the reguired knowledge of its usage is more likely to commit suicide, than a person that does not own a firearm and does not know how to use one. Another example would be a person that has access and knowledge to drugs, that can be used in ending ones life. This second example is backed by resereach, that has shown that medical professionals such as anesthesiologists have elevated suicide rates. (Klonsky and May, 2016).

5. Neuroimaging can be used to analyze the brain

Neuroimaging is a concept, that contains a group of different technologies and techniques that can be used to gain information from the function of a brain. Neuroimaging can be divided into structural imaging, and functional imaging.

Structural imaging gives information on the structure of the nervous system and can be used in diagnostics of large scale intracranial diseases, such as different tumors and trauma. In psychiatry this can be used for example to diffrentiate between somatic and psychiatric causes of psychosis.

Funtional imaging can be used to diagnose metabolic diseases and cellular changes on a finer scale. Functional imaging can also used to study the effects of pain stimulus on the brain.

Psychiatric disorders can be investigated with a variety of neuroimaging techniques and the most important tehcnologies in this regard are functional neuroimaging tehcnigues: magnetic resonance imaging (fMRI), positron emission tomography (PET) and single photon emission tomography (SPECT).

5.1. How is neuroimaging used in psychiatry?

In psychiatry neuroimaging can be used to as an aide in diagnosis and in the development of new medications. The way structural neuroimaging can be used in diagnostics is firstly by detecting structural lesions and tumors, that could cause psychosis and secondly in differentiating depression from clinically similar states of mind caused by neurodegenerative disorders or brain tumors (Masdeu, 2011). Psychiatric diagnoses are usually caused by an neuronal network dysfunction (American Psychiatric Association, 2000) and these neuronal network abnormalities tend to be heterogenous in their neurobiology (Markou et al., 2009). However it has been shown that the diagnosis of a patient is not accurate, if only neuroimaging is used (Masdeu, 2011).

While structural imaging focuses on the structure of the nervous system, functional imaging can be used to study for example the activation of different brain areas in reaction to a certain stimulus or stimuli. Functional imaging is disucssed more in the following chapters: 5.1.1. and 5.1.2.

5.1.1 Functional neuroimaging and different forms of pain

With functional neuroimaging it is possible to study the activation of different areas of the brain in response to the pain stimulus. All types of pain activate the anterior cingulate cortex (ACC), insula and the prefrontal cortex (PFC). There is some evidence to suggest, that somatosensory cortices may be uniquely activated in physical pain (Mee et al., 2016, Meerwijk et al., 2013). Brain areas involved in psychological pain are in the medial subcortical area. More spesifically the areas activated by psychological pain include ACC, posterior cingulate cortex (PCC), thalamus, basal ganglia (putamen and caudate), cerebellum and cerebellar vermis. (Meerwijk et al., 2013).

Meerwijk et al. (Meerwijk et al., 2013) found that there is overlap between the neural networks of psychological and physical pain. Furthermore according to Meerwijk, the role of insula, caudate and putamen are markedly reduced during psychological pain (Meerwijk et al., 2013). A study by Biro (Biro 2010) has found that physical and psychological pain activate similar areas of the brain. Biros study is critiqued on the fact, that it does not asses actual psychological pain. (Meerwick et al., 2016). In addition to physical and psychological pain activating partially different brain areas, the areas of the brain also differ according to the temporal nature of the pain. Insula is activated in acute pain, while chronic pain causes a lesser activation of this brain area. (Apkarian et al., 2005).

5.1.2 Functional neuroimaging and suicidal acts

There has been a number of studies, that were able to identify potential neural conncectivity differences between suicide attempters and suicide ideators. Minzenberg and his/her collegues found that the conncectivity patterns of dorsal anterior cingulate cortex, imaged during a cognitive control task, differentiated suicide attempters from suicide ideators (Minzenberg et al., 2015a).

In a second study Minzenberg et al found that the right ventrolateral prefrontal cortex differentiated suicide attempters from suicide ideators (Minzenberg et al., 2015 b). Additionally suicidal ideation was associated with higher activation in the orbitofrontal cortex, dorsal striatum and rostral insula. Suicide attempt was associated with a lower activity in midline parietal regions (Minzenberg et al, 2015b).

A third study by Minzenberg et al found that the left hemisphere supplementary motor area, premotor cortex, presupplementary motor area and dorsolateral prefrontal cortex were activated in suicide attempters (Minzenberg et al., 2015c).

These three studies by Minzenberg et al. are interesting and warrant further research. They are limited by the number of samples included in the studies. In these studies people are grouped into suicide attempters and suicide ideators and the sample sizes are less than 20 for each group.

6. Medicine affecting the opioid system could prove to be useful in treating psychological pain

6.1 The role of the endogenous opioid system in pain and NSSI

The endogenous opioid system (EOS) is involved in the regulaiton of emotions and pain and has been proposed to be connceted to non-suicidal self injury (NSSI). Endogenous opioids are peptides, that can interact with the opiate receptors of cell membranes and thus produce analgesic effects. Endogenous opioids are grouped into four different classes: B-endorphin, dynorphins, endomorphins and enkephalins (Herz, 1997). The opiate receptors on the cell membranes are grouped into three different receptor types: mu-, delta- and kappa-receptors (Dhawan, 1996). The analgesic properties of opioids is thought to arise from an increased activity of mu- and delta receptors (Rizvi et al., 2017). One of the most known opiates, morphine, works by binding and activating the mu opioid receptor (Rizvi et al., 2017).

Bresin and Gordon (Bresin and Gordon, 2013) found two main explanations for the conneciton between NSSI and EOS. One explanation is based on B-endorphin and enkephalin levels of the NSSI individiuals. In NSSI individuals the resting level of these peptides may be lower than in individuals not partaking in NSSI. The low level of B-endorphin and enkephalin is thought to augment the reward value of mu- and delta-receptors and as a result the actual reward linked to the NSSI activity (Rizvi et al., 2017). The second explanation is based on the release of B-endorphin and enkephalin during the act of NSSI. These peptides are thought to work as an affect regulator during NSSI, so they could decrease negative affects or increase positive affects (Rizvi et al., 2017). (Bresin and Gordon, 2013).

6.2 Can ultra-low-dose buprenorphine be used to treate suicidality?

Pharmaceutical treatment of suicidality is a challenge, because most of the pharmaceutics used have severe problems. Generally the pharmaceutics used to treat suicidality can be grouped into antidepressants, atypical antipsychotics, ketamine and opioids, namely buprenorphine. (Yovell et al., 2016).

Antidepressants, like SSRIs, may relieve suicidal ideation, but this usually takes several weeks. Lithium and atypical antipsychotics have also been used to decrease suicidal ideation, but generally these pharmaceuticals tend to have significant side effects. Ketamine is effective and quick acting treatment for suicidal ideation and depression, but requires repeated administration under medical supervision. (Yovell et al., 2016).

Buprenorphine is one of the most interesting pharmaceuticals being tested for the treatment of suicidal ideation. Buprenorphine is part of the opioid group of pharmaceuticals. Earlier opioids were actually used to treat depression from about 1850 to 1956, but were replaced by standard antidepressants when they became available, at least partly because of the addictive potential of the opioids and the possibility of lethality in an overdose situation (Tenore, 2008).

Buprenorphine works by affecting several different mechanisms, like depression and psychological pain, that contribute to suicidal ideation. Buprenorphine is thought to affect depression in a reducing manner by inhibiting seperation distress, which is shown in animal models to cause depression(Panskepp and Solms, 2012). One of the larger groups among suicide ideators and attempters is patients with borderline personality disorder (BPD). It has been shown, that suicidality tends to increase in patients with BPD after interpersonal rejections. Interpersonal rejections and interpersonal losses are also a leading cause for suicidal acts among patients receiving psychotherapy (Richards, 1999). Patients with BPD have also been shown to have abnormalities in their endogenous opioid system. Some studies have shown mental pain to be a strong variable associated with suicidality.

In 2016 Yovell et al. (Yovell et al., 2016) made a clinical study, in which the objective was to see how suicidal people would react to buprenorphine. Yovells study was performed, in the industry standard, as a multisite randomized double-blind placebo-controlled trial and the results were that the use of ultra-low-dose sublingual burpenorphine was associated with decreased suicidal ideation – and the treatment could also be stopped with no withdrawdal synptoms.

The differences found in the study made by Yovell et al., between buprenorphine group and the control group can be grouped into significant differences and non-significant differences. Significant differences were in adverse events, of which the buprenorphine group had more, and a significant reduction in the Beck Suicide Ideation Scale (SBIS). (Yovell et al., 2016).

Adverse events reported by the participants were 77.2% for the buprenorphine group and 54.8% for the placebo group ($p=0.03$). This difference was statistically relevant. The adverse events reported were fatigue, nausea, dry mouth and constipation. Despite these adverse events the treatment was considered to be well tolerated. Discontinuation percentage of the patients in this study due to adverse effects was 22.8% for the buprenorhphine group and 16.1% for the placebo group. (Yovell et al., 2016).

The buprenorphine group had a statistically significant reduction in the Beck Suicide Ideation Scale (BSIS), when compared to the placebo group. The results were analyzed after two and four weeks and the opioid group had a greater reduction in BSIS scores in both of these time windows. Intrestingly some of the items in Suicide Propability Scale yielded significant results, even though the reduction in the score given by the Suicide Probality Scale was considered to be lower, but not by a significant amount, for the buprenorphine group. In theme of this paper the most important item was item 25 of the Suicide Propability Scale. Item 25 demonstrated a statistically significant reduction in the level of mental pain for the buprenorphine group. (Yovell et al., 2016).

For the theme of psyache the most important non-significant differences found by Yovell et al. were a reduced score in the Suicide Propability Scale for the buprenorphine group. The buprenorphine group also had a lower Beck Depression Inventory scores than the placebo group, but again the result was not statistically significant. Reduction in depressive symptoms was considered to be smaller than the reduction in suicidal ideation.

6.3 Non-direct evidence on the connection of the opioid system to suicide attempts

There is also non direct evidence of the role of the opioid system in suicide attempters. For example opioid analgesics are consumed in larger numbers by people who have attempted suicide (Olie, 2013) and one of the explanations for this finding is that the opiate use may have started as a self-medication for suicidality.

Postmortem studies of deaths by suicide have some interesting, but partly contradictory findings. A study by Gross-Isseroff et al., (Gross-Isseroff et al., 1990) found incrased mu-receptor density in the frontal cortex and caudate of death-by-suicide cadavers. Then again Scarr et al.,(Scarr et al., 2012) studied the cadavers of schizophrenic patients, who had died by suicide, and demonstrated a decrease in mu-opioid receptor density in the frontal cortex and caudate (Scarr et al., 2012). The studies by Gross-Isseroff and Scarr all had a small sample size of around 15 patients per group, so these findings could also be explained partly by chance. Because of the small sample size it is not possible to make strong conclusions one way or the other, but these interesting findings surely warrant further study.

7. Discussion

7.1 Psychological pain needs to be addressed

Psychological pain is connected to suicidal behavior, as has been demonstrated by a variety of scientists (Shneidman, 1996; Baumeister, 1990, Troister and Holden 2010). As death by suicide is a significant cause of death in the world, this conncetion between suicidality and psychological pain cannot be ignored – lives are literally lost daily. They could be saved if psychological pain and its treatment would be better understood and implemented.

Psychological pain doesn't have clear diagnostic criteria. As demonstrated by American Psychiatric Association in 2003 (American Psychiatric Association, 2003) psychological pain is thought to be quite common among people with psychiatric diseases or who have suffered remarkable adverse life events. Considering the undesirable activities connected with psychological pain, such as a suicide or NSSI, not to mention the individual suffering experienced by people who are ailed by psyache, it is clear that more research, clear diagnostic criteria and clear treatment plans based on Evidence Based Medicine are sorely needed.

In order for the general clinicians to be familiar enough with psychological pain to be able to treat it, a lot of work has to be done. At the moment there is no specific treatment for psychological pain. Yovell et al., (Yovell et al., 2016) demonstrated the usage of ultra low dose sublingual bupinorphine in treatment of psychological pain. We need more studies like this, to be better able to help people suffering from psychological pain. These studies could include different validated treatment plans that could vary depending on the assertment of symptoms of the patient. One huge problem is that the results of a failed treatment, or even placebo treatment, can lead to unwelcome results, since the connection between psychological pain and suicidal behavior is strong (Shneidman, 1996; Baumeister, 1990, Troister and Holden 2010).

The scales of measuring psychological pain are many and vary from one another in significant ways. Because of this it seems to me that more research, maybe researching the validity of the scales relative to each other, is needed. Many of the other, more known psychiatric ailments have a variety of different scales, but usually one of these scales is considered to be golden standard,

atleast among general practicioners. I believe psychological pain needs such a scale, one that is readily available, easy to use, fast to fill and analyze an well known.

From the scales made and used in the quantification of psychological pain my personal favourite is The Mee-Bunney Psychological Pain Assessment Scale (MBPPAS).The questions in MBPPAS have been validated by exsisting scales used in treatment of different psychiatric ailments and its Cronbach Alpha value is considered to be good. One additional strength of MBPPAS is that it is designed to be fillable in five minutes, so it would be suitable for usage in general practices. The MBPPAS is relatively new scale, so more research is required.

8. Conclusion

Psychological pain is a different concept from physical pain, as demonstrated for example by the neuronal network studies (Meerwijk et al., 2013). Psychological pain is also a different concept from depression and hopelessness and it is strongly correlated with suicidal acts, as demonstrated for example by the 3ST (Klonsky and May, 2016). In addition to neural network studies psychological pain can be quantified for example by the use of questionnaires, of which there are several.

Ideation-to-action framework is a collection of the most modern and sophisticated suicide models. The latest addition to this group is the 3ST by Klonsky and May (Klonsky and May, 2015). Pain is a central concept in the 3ST, as in 3ST the first step toward suicidal ideation begins with pain, the second step is taken after pain exceeds connectedness and the third step can occur for example when one becomes habituated with pain.

Meta-analysis by Klonsky and May (Klonsky and May, 2016) compared the variables of depression and hopelessness with suicide attempters to suicide ideators. The result was that the effect sizes for depression and hopelessness dropping to near zero. Klonsky and May emphasize that this does not mean that hopelessness or depression do not have their effect on suicidal ideation or suicidal acts. In their theory hopelessness and depression contribute to suicidal acts and suicidal ideation throught their effect on pain and/or disturbed conncetedness. (Klonsky and May, 2016).

At the moment of writing there is no specific medication available for psychological pain. In 2016 Yovell et al. (Yovell et al., 2016) made a study on the usage of ultra low dose sublingual bupinorphine, that proved to be effective in reducing the level of psychological pain as well as suicidal ideation (Yovell et al., 2016). This can be explained by the fact that bupinorphine has been validated as a effective medicine for physical pain and physical pain and psychological pain share some common neural networks.

Since psychological pain and suicidal acts are closely related, one way to treat psychological pain could be through treatments that have been proven to be effective in treating suicidal acts. There is some evidence suggesting that therapy, in the form of cognitive and behavioral therapy, can decrease the risk of new suicide attempts among people, with previous suicide attempts (O'Connor and Nock, 2014). One explanation for this could be that the cognitive and behavioral therapies affect the level of psychological pain experienced by the patient. Needless to say we need more research focusing on the effect of these therapies on people who suffer from psychological pain.

9. References

(1) American Psychiatric Association editor. Diagnostic and statistical manual of mental disorders. 4th ed. ed. Washington: American Psychiatric Press; 2000.

(2) American psychiatric association, Arlington. Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviors. 2003.

(3) Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 2005 Aug;9(4):463-484.

(4) Baumeister RF. Suicide as escape from self. Psychol Rev 1990 Jan;97(1):90-113.

(5) Beck A, Brown G, Steer R. Prediction of eventual suicide in psychiatric inpatients by clinical ratings of hopelessness. . Journal of Consulting and Clinical Psychology 1989;57(2):309-310.

(6) Bion W,. Attention and Interpretation. London: Marcsfield Library; 1970.

(7) Biro D. Is there such a thing as psychological pain? And why it matters. Cult Med Psychiatry. 2010;34(4):658-667.

(8) Bolger E. **Grounded Theory Analysis of Emotional Pain**. Psychotherapy Research 1999;9(3):342-342-362.

(9) Bolger E, Shneidman ES. Grounded theory analysis of emotional pain; Perspectives on suicidology. Further reflections on suicide and psychache. Suicide Life Threat Behav 1998 Fall;9; 28(3):342; 245-362; 250.

(10) Borges G., Nock M, et al. 2010 Journal of Clinical Psychiatry;71(12):1617-1628.

(11) Bresin K, Gordon K. Endogenous opioids and nonsuicidal self-injury: a mechanism of affect regulation. Neuroscience & Biobehavioral Reviews 2013;37(3):374-383.

(12) Cassell EJ. Diagnosing suffering: a perspective. Ann Intern Med 1999 Oct 5;131(7):531-534.

(13) Cavanagh J, Carson A, Sharpe M, Lawrie S. Psychological autopsy studies of suicide: a systematic review. . Psychological Medicine 2003;33(3):395-405.

(14) Change citation format Nock, M., Borges, G., Bromet, E., Alonso, J., Angermeyer, M., Beautrais, A., . . . Williams, D. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. British Journal of Psychiatry 2008;192(2):98-105.

(15) Courtet P, Olie E. Neurobiology of suicidal behavior and social stress. J Neurosci Res 2020 Apr;98(4):579-580.

(16) DeLisle M, Holden R. Differentiating Between Depression, Hopelessness, and Psychache in University Undergraduates. Measurement and Evaluation in Counseling and Development. 2009;42(1):46-63.

(17) Dhawan B, Cesselin F, Raghubir R, Reisine T, Bradley P, Portoghese P, et al. International Union of Pharmacology. XII. Classification of opioid receptors. Pharmagological Reviews 1996;48(4):567-592.

(18) Ducasse D, Holden RR, Boyer L, Artero S, Calati R, Guillaume S, et al. Psychological Pain in Suicidality: A Meta-Analysis. J Clin Psychiatry 2018 May/Jun;79(3):10.4088/JCP.16r10732.

(19) Fitzpatrick K, Irwin J, LaGory M, Ritchey F. Just Thinking about it: Social Capital and Suicide Ideation among Homeless Persons. Journal of Health Psychology 2007;12(5):750-760.

(20) Flamenbaum, R., & Holden, R. R. Psychache as a mediator in the relationship between perfectionism and suicidality. Journal of Counseling Psychology 2007;54(1):51-61.

(21) Flamenbaum R, Holden R,R, Mee S, Bunney BG, Reist C, Potkin SG, et al. Psychache as mediator in the relationship between perfectionism and suicidality; Psychological pain: a review of evidence. J Psychiatr Res 2006 Dec;54; 40(1; 8):51; 680-61; 690.

(22) Fleming M, Mills JF, Green K, Reddon JR. Distinction between mental pain and psychic suffering as separate entities in the patient's experience; An evaluation of the Psychache Scale on an offender population. Suicide Life Threat Behav 2005 Oct;15; 35(4; 5):195; 570-200; 580.

(23) Frankl V,. Man's Search for Meaning. New York: First Washington Square Press; 1963.

(24) Gabilondo A, Meana J, García-Sevilla J. Increased density of mu-opioid receptors in the postmortem brain of suicide victims. Brain Research 1995;682(1-2):245-50.

(25) Goueslard K, Petit JM, Cottenet J, Chauvet-Gelinier JC, Jollant F, Quantin C. Increased Risk of Rehospitalization for Acute Diabetes Complications and Suicide Attempts in Patients With Type 1 Diabetes and Comorbid Schizophrenia. Diabetes Care 2018 Nov;41(11):2316-2321.

(26) Gross-Isseroff R, Dillon K, Israeli M, Biegon A. Regionally selective increases in mu opioid receptor density in the brains of suicide victims. Brain Research 1990;530(2):312-316.

(27) Guimaraes R, Fleming M, Cardoso MF. Validation of the Orbach & Mikulincer Mental Pain Scale (OMMP) on a drug addicted population. Soc Psychiatry Psychiatr Epidemiol 2014 Mar;49(3):405-415.

(28) Gvion Y, Horresh N, Levi-Belz Y, Fischel T, Treves I, Weiser M, et al. Aggression-impulsivity, mental pain, and communication difficulties in medically serious and medically non-serious suicide attempters. Compr Psychiatry 2014 Jan;55(1):40-50.

(29) Herz A. Endogenous opioid systems and alcohol addiction
. Psychopharmacology 1997;129(2):99-111.

(30) Holden R, Mehta K, Cunningham E, McLeod L. Development and preliminary validation of a scale of psyache. Canadian Journal of Behavioural Science 2001;33(4):224-232.

(31) International Association for the Study of,Pain,, Bion W, Frankl V,. Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy; Attention and Interpretation; A Man's Search for Meaning. Pain; London: Marcsfield Library; New York, First Washington Square Press 1979; 1970; 1963;6:249.

(32) International Association for the Study of,Pain,, Bion W, Frankl V,. Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy; Attention and Interpretation; A Man's Search for Meaning. Pain; London: Marcsfield Library; New York, First Washington Square Press 1979; 1970; 1963;6:249.

(33) Joiner T. Why people die by suicide. : Harvard University Press; 2005.

(34) Jollant F, Lemogne C, Fossati P. Self-reference in suicidal behaviour. Cogn Neuropsychiatry 2017 Nov;22(6):486-494.

(35) Jollant F, Voegeli G, Kordsmeier NC, Carbajal JM, Richard-Devantoy S, Turecki G, et al. A visual analog scale to measure psychological and physical pain: A preliminary validation of the PPP-VAS in two independent samples of depressed patients. Prog Neuropsychopharmacol Biol Psychiatry 2019 Mar 2;90:55-61.

(36) Jollant F, Voegeli G, Kordsmeier NC, Carbajal JM, Richard-Devantoy S, Turecki G, et al. A visual analog scale to measure psychological and physical pain: A preliminary validation of the PPP-VAS in two independent samples of depressed patients. Prog Neuropsychopharmacol Biol Psychiatry 2019 Mar 2;90:55-61.

(37) Jollant F, Wagner G, Richard-Devantoy S, Kohler S, Bar KJ, Turecki G, et al. Neuroimaging-informed phenotypes of suicidal behavior: a family history of suicide and the use of a violent suicidal means. Transl Psychiatry 2018 Jun 19;8(1):120-018-0170-2.

(38) Klonsky E, May A. Differentiating suicide attempters from suicide ideators: a critical frontier for suicidology research. Suicide and Life Threatening Behavior 2014;44(1):1-5.

(39) Klonsky E, May A. Rethinking impulsivity in suicide. Suicide and Life Threatening Behavior 2010;40(6):612-619.

(40) Klonsky E, May A, Glenn C. The relationship between nonsuicidal self-injury and attempted suicide: converging evidence from four samples. Journal of Abnormal Psychology 2013;122(1):231-237.

(41) Klonsky E, May A, Saffer B. Suicide, Suicide Attempts and Suicidal Ideation. Annual Review of Clinical Psychology 2016;12:307-330.

(42) Klonsky ED, May AM. What Distinguishes Suicide Attempters From Suicide Ideators? A Meta-Analysis of Potential Factors. Clinical Psychology: Science and Practice 2016;23(1):5-20.

(43) Levi Y, Horesh N, Fischel T, Treves I, Or E, Apter A. Mental pain and its communication in medically serious suicide attempts: an "impossible situation". . J Affect Disord. 2008;111(2-3):244-250.

(44) Li H, Fu R, Zou Y, Cui Y. Predictive Roles of Three-Dimensional Psychological Pain, Psychache, and Depression in Suicidal Ideation among Chinese College Students. Front Psychol 2017 Sep 12;8:1550.

(45) Loeser JD. Pain and suffering. Clin J Pain 2000 Jun;16(2 Suppl):S2-6.

(46) Macdonald G, Leary MR. Why does social exclusion hurt? The relationship between social and physical pain. Psychol Bull 2005 Mar;131(2):202-223.

(47) Markou A, Chiamulera C, Geyer M, Tricklebank M, Steckler T. Removing obstacles in neuroscience drug discovery: the future path for animal models. Neuropsychopharmacology 2009;34(1):74-89.

(48) Masdeu J. Neuroimaging in Psychiatric Disorders. Neurotherapeutics 2011;8(1):93-102.

(49) Mee S, Bunney B, Bunney W, Hetrick W, Potkin S, Reist C. Assessment of psychological pain in major depressive episodes. . J Psychiatr Res. 2011;45(11):1504-1510.

(50) Mee S, Bunney B, Reist C, Potkin S, Bunney W. Psychological pain: a review of evidence. . J Psychiatr Res. 2006;40(8):680-690.

(51) Meerwijk EL, Ford JM, Weiss SJ. Brain regions associated with psychological pain: implications for a neural network and its relationship to physical pain. Brain Imaging Behav 2013 Mar;7(1):1-14.

(52) Meerwijk EL, Weiss SJ. (1) American Psychiatric Association editor. Diagnostic and statistical manual of mental disorders. 4th ed. ed. Washington: American Psychiatric Press; 2000.

(2) American psychiatric association, Arlington. Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviors. 2003.

(3) Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 2005 Aug;9(4):463-484.

(4) Baumeister RF. Suicide as escape from self. Psychol Rev 1990 Jan;97(1):90-113.

(5) Beck A, Brown G, Steer R. Prediction of eventual suicide in psychiatric inpatients by clinical ratings of hopelessness. . Journal of Consulting and Clinical Psychology 1989;57(2):309-310.

(6) Bion W,. Attention and Interpretation. London: Marcsfield Library; 1970.

(7) Biro D. Is there such a thing as psychological pain? And why it matters. Cult Med Psychiatry. 2010;34(4):658-667.

(8) Bolger E. Grounded Theory Analysis of Emotional Pain. Psychotherapy Research 1999;9(3):342-342-362.

(9) Bolger E, Shneidman ES. Grounded theory analysis of emotional pain; Perspectives on suicidology. Further reflections on suicide and psychache. Suicide Life Threat Behav 1998 Fall;9; 28(3):342; 245-362; 250.

(10) Borges G., Nock M, et al. 2010 Journal of Clinical Psychiatry;71(12):1617-1628.

(11) Bresin K, Gordon K. Endogenous opioids and nonsuicidal self-injury: a mechanism of affect regulation. Neuroscience & Biobehavioral Reviews 2013;37(3):374-383.

(12) Cassell EJ. Diagnosing suffering: a perspective. Ann Intern Med 1999 Oct 5;131(7):531-534.

(13) Cavanagh J, Carson A, Sharpe M, Lawrie S. Psychological autopsy studies of suicide: a systematic review. . Psychological Medicine 2003;33(3):395-405.

(14) Change citation format Nock, M., Borges, G., Bromet, E., Alonso, J., Angermeyer, M., Beautrais, A., . . . Williams, D. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. British Journal of Psychiatry 2008;192(2):98-105.

(15) Courtet P, Olie E. Neurobiology of suicidal behavior and social stress. J Neurosci Res 2020 Apr;98(4):579-580.

(16) DeLisle M, Holden R. Differentiating Between Depression, Hopelessness, and Psychache in University Undergraduates. Measurement and Evaluation in Counseling and Development. 2009;42(1):46-63.

(17) Dhawan B, Cesselin F, Raghubir R, Reisine T, Bradley P, Portoghese P, et al. International Union of Pharmacology. XII. Classification of opioid receptors. Pharmagological Reviews 1996;48(4):567-592.

(18) Ducasse D, Holden RR, Boyer L, Artero S, Calati R, Guillaume S, et al. Psychological Pain in Suicidality: A Meta-Analysis. J Clin Psychiatry 2018 May/Jun;79(3):10.4088/JCP.16r10732.

(19) Fitzpatrick K, Irwin J, LaGory M, Ritchey F. Just Thinking about it: Social Capital and Suicide Ideation among Homeless Persons. Journal of Health Psychology 2007;12(5):750-760.

(20) Flamenbaum, R., & Holden, R. R. Psychache as a mediator in the relationship between perfectionism and suicidality. Journal of Counseling Psychology 2007;54(1):51-61.

(21) Flamenbaum R, Holden R,R, Mee S, Bunney BG, Reist C, Potkin SG, et al. Psychache as mediator in the relationship between perfectionism and suicidality; Psychological pain: a review of evidence. J Psychiatr Res 2006 Dec;54; 40(1; 8):51; 680-61; 690.

(22) Fleming M, Mills JF, Green K, Reddon JR. Distinction between mental pain and psychic suffering as separate entities in the patient's experience; An evaluation of the Psychache Scale on an offender population. Suicide Life Threat Behav 2005 Oct;15; 35(4; 5):195; 570-200; 580.

(23) Frankl V,. Man's Search for Meaning. New York: First Washington Square Press; 1963.

(24) Gabilondo A, Meana J, García-Sevilla J. Increased density of mu-opioid receptors in the postmortem brain of suicide victims. Brain Research 1995;682(1-2):245-50.

(25) Goueslard K, Petit JM, Cottenet J, Chauvet-Gelinier JC, Jollant F, Quantin C. Increased Risk of Rehospitalization for Acute Diabetes Complications and Suicide Attempts in Patients With Type 1 Diabetes and Comorbid Schizophrenia. Diabetes Care 2018 Nov;41(11):2316-2321.

(26) Gross-Isseroff R, Dillon K, Israeli M, Biegon A. Regionally selective increases in mu opioid receptor density in the brains of suicide victims. Brain Research 1990;530(2):312-316.

(27) Guimaraes R, Fleming M, Cardoso MF. Validation of the Orbach & Mikulincer Mental Pain Scale (OMMP) on a drug addicted population. Soc Psychiatry Psychiatr Epidemiol 2014 Mar;49(3):405-415.

(28) Gvion Y, Horresh N, Levi-Belz Y, Fischel T, Treves I, Weiser M, et al. Aggression-impulsivity, mental pain, and communication difficulties in medically serious and medically non-serious suicide attempters. Compr Psychiatry 2014 Jan;55(1):40-50.

(29) Herz A. Endogenous opioid systems and alcohol addiction
. Psychopharmacology 1997;129(2):99-111.

(30) Holden R, Mehta K, Cunningham E, McLeod L. Development and preliminary validation of a scale of psyache. Canadian Journal of Behavioural Science 2001;33(4):224-232.

(31) International Association for the Study of,Pain,, Bion W, Frankl V,. Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy; Attention and Interpretation; A Man's Search for Meaning. Pain; London: Marcsfield Library; New York, First Washington Square Press 1979; 1970; 1963;6:249.

(32) International Association for the Study of,Pain,, Bion W, Frankl V,. Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy; Attention and Interpretation; A Man's Search for Meaning. Pain; London: Marcsfield Library; New York, First Washington Square Press 1979; 1970; 1963;6:249.

(33) Joiner T. Why people die by suicide. : Harvard University Press; 2005.

(34) Jollant F, Lemogne C, Fossati P. Self-reference in suicidal behaviour. Cogn Neuropsychiatry 2017 Nov;22(6):486-494.

(35) Jollant F, Voegeli G, Kordsmeier NC, Carbajal JM, Richard-Devantoy S, Turecki G, et al. A visual analog scale to measure psychological and physical pain: A preliminary validation of the PPP-VAS in two independent samples of depressed patients. Prog Neuropsychopharmacol Biol Psychiatry 2019 Mar 2;90:55-61.

(36) Jollant F, Voegeli G, Kordsmeier NC, Carbajal JM, Richard-Devantoy S, Turecki G, et al. A visual analog scale to measure psychological and physical pain: A preliminary validation of the PPP-VAS in two independent samples of depressed patients. Prog Neuropsychopharmacol Biol Psychiatry 2019 Mar 2;90:55-61.

(37) Jollant F, Wagner G, Richard-Devantoy S, Kohler S, Bar KJ, Turecki G, et al. Neuroimaging-informed phenotypes of suicidal behavior: a family history of suicide and the use of a violent suicidal means. Transl Psychiatry 2018 Jun 19;8(1):120-018-0170-2.

(38) Klonsky E, May A. Differentiating suicide attempters from suicide ideators: a critical frontier for suicidology research. Suicide and Life Threatening Behavior 2014;44(1):1-5.

(39) Klonsky E, May A. Rethinking impulsivity in suicide. Suicide and Life Threatening Behavior 2010;40(6):612-619.

(40) Klonsky E, May A, Glenn C. The relationship between nonsuicidal self-injury and attempted suicide: converging evidence from four samples. Journal of Abnormal Psychology 2013;122(1):231-237.

(41) Klonsky E, May A, Saffer B. Suicide, Suicide Attempts and Suicidal Ideation. Annual Review of Clinical Psychology 2016;12:307-330.

(42) Klonsky ED, May AM. What Distinguishes Suicide Attempters From Suicide Ideators? A Meta-Analysis of Potential Factors. Clinical Psychology: Science and Practice 2016;23(1):5-20.

(43) Levi Y, Horesh N, Fischel T, Treves I, Or E, Apter A. Mental pain and its communication in medically serious suicide attempts: an "impossible situation". . J Affect Disord. 2008;111(2-3):244-250.

(44) Li H, Fu R, Zou Y, Cui Y. Predictive Roles of Three-Dimensional Psychological Pain, Psychache, and Depression in Suicidal Ideation among Chinese College Students. Front Psychol 2017 Sep 12;8:1550.

(45) Loeser JD. Pain and suffering. Clin J Pain 2000 Jun;16(2 Suppl):S2-6.

(46) Macdonald G, Leary MR. Why does social exclusion hurt? The relationship between social and physical pain. Psychol Bull 2005 Mar;131(2):202-223.

(47) Markou A, Chiamulera C, Geyer M, Tricklebank M, Steckler T. Removing obstacles in neuroscience drug discovery: the future path for animal models. Neuropsychopharmacology 2009;34(1):74-89.

(48) Masdeu J. Neuroimaging in Psychiatric Disorders. Neurotherapeutics 2011;8(1):93-102.

(49) Mee S, Bunney B, Bunney W, Hetrick W, Potkin S, Reist C. Assessment of psychological pain in major depressive episodes. . J Psychiatr Res. 2011;45(11):1504-1510.

(50) Mee S, Bunney B, Reist C, Potkin S, Bunney W. Psychological pain: a review of evidence. . J Psychiatr Res. 2006;40(8):680-690.

(51) Meerwijk EL, Ford JM, Weiss SJ. Brain regions associated with psychological pain: implications for a neural network and its relationship to physical pain. Brain Imaging Behav 2013 Mar;7(1):1-14.

(52) Meerwijk EL, Weiss SJ. **Toward a Unifying Definition of Psychological Pain**. Journal Loss and Trauma 2011;16(5):402-402-412.

(53) Meerwijk E,L, Biro D. Toward a Unifying Definition of Psychological Pain; Is there such a thing as psychological pain? And why it matters. Cult Med Psychiatry 2010 Dec;16; 34(5; 4):402; 658-412; 667.

(54) Mills J, Green K, Reddon J. An evaluation of the Psychache Scale on an offender population. Suicide Life Threat Behav. 2005;35(5):570-580.

(55) Minzenberg M, Lesh T, Niendam T, Yoon J, Cheng Y, Rhoades R, et al. Frontal motor cortex activity during reactive control is associated with past suicidal behavior in recent-onset schizophrenia. Crisis 2015b;36:363-370.

(56) Minzenberg M, Lesh T, Niendam T, Yoon J, Cheng Y, Rhoades R, et al. Conflict-related anterior cingulate functional connectivity is associated with past suicidal ideation and behavior in recent-onset schizophrenia. Journal of Psychiatric Research 2015a;65:95-101.

(57) Minzenberg M, Lesh T, Niendam T, Yoon J, Cheng Y, Rhoades R, et al. Control-related frontal-striatal funciton is associated with past suicidal ideation and behavior in patients with recent-onset psychotic major mood disorders. Journal of Affective Disorders 2015c;188:202-209.

(58) Nock M, Park JM, Finn C, Deliberto T, Dour H, Banaji M. Measuring the suicidal mind: implicit cognition predicts suicidal behavior. Psychological science 2010;21(4):511-517.

(59) O'Connor R, Nock M. The psychology of suicidal behaviour. Lancet Psychiatry 2014;1.

(60) Olie E, Courtet P, Poulain V, Guillaume S, Ritchie K, Artero S. History of suicidal behaviour and analgesic use in community-dwelling elderly. Psychotherapy and Psychosomatics 2013;82(5):341-343.

(61) Orbach I, Mikulincer M, Sirota P, Gilboa-Schechtman E. Mental pain: a multidimensional operationalization and definition. Suicide Life Threat Behav 2003 Fall;33(3):219-230.

(62) Pachkowski MC, May AM, Tsai M, Klonsky ED. A Brief Measure of Unbearable Psychache. Suicide Life Threat Behav 2019 Dec;49(6):1721-1734.

(63) Panksepp J, Solms M. What is neuropsychoanalysis? Clinically relevant studies of the minded brain. Trends in Cognitive Sciences 2012;16(1):6-8.

(64) Patterson A, Holden R. Psychache and suicide ideation among men who are homeless: a test of Shneidman's model. Suicide and Life Threatening Behavior 2012;42(2):147-156.

(65) Patterson A,A, Holden R,R, Mee S, Bunney BG, Bunney WE, Hetrick W, et al. Psychache and Suicide Ideation among Men Who Are Homeless: A Test of Shneidmanâ€™s Model; Assessment of psychological pain in major depressive episodes. J Psychiatr Res 2011 Nov;42; 45(2; 11):1504-1510.

(66) Pereira EJ, Kroner DG, Holden RR, Flamenbaum R. Testing Shneidman's model of suicidality in incarcerated offenders and in undergraduates. Personality and Individual Differences 2010;49(8):912-917.

(67) Pompili M, Lester D, Leenaars AA, Tatarelli R, Girardi P. Psychache and suicide: a preliminary investigation. Suicide Life Threat Behav 2008 Feb;38(1):116-121.

(68) Richards B. Suicide and internalised relationships: A study from the perspective of psychotherapists working with suicidal patients. British Journal of Guidance & Counselling 1998;27(1):85-98.

(69) Rizvi SJ, Iskric A, Calati R, Courtet P. Psychological and physical pain as predictors of suicide risk: evidence from clinical and neuroimaging findings. Curr Opin Psychiatry 2017 Mar;30(2):159-167.

(70) Scarr E, Money T, Pavey G, Neo J, Dean B. Mu opioid receptor availability in people with psychiatric disorders who died by suicide: a case control study. BMC Psychiatry. 2012;12(126).

(71) Schutt R, Meschede T, Rierdan J. Distress, Suicidal Thoughts, and Social Support Among Homeless Adults*. Journal of Health and Social Behavior 1994;35(2):134-142.

(72) Shneidman ES. The suicidal mind. Oxford University Press 1996.

(73) Shneidman ES. Suicide as psyache. Journal of Nervous and Mental Disease 1993(181):147-149.

(74) Shneidman E. Perspectives on suicidology. Further reflections on suicide and psychache. Suicide Life Threat Behav. 2998;28(3):245-250.

(75) Shneidman ES. The psychological pain assessment scale. Suicide Life Threat Behav 1999 Winter;29(4):287-294.

(76) Shneidman ES. Suicide as psychache. J Nerv Ment Dis 1993 Mar;181(3):145-147.

(77) Shneidman ES. A possible classification of suicidal acts based on Murray's need system. Suicide Life Threat Behav 1980 Fall;10(3):175-181.

(78) Smith A, Ribeiro J, Mikolajewski A, Taylor J, Joiner T, Iacono W. An examination of environmental and genetic contributions to the determinants of suicidal behavior among male twins.
. Psychiatry Research 2012;197(1-2):60-65.

(79) Smith M, Edwards R, Robinson R, Dworkin R. Suicidal ideation, plans, and attempts in chronic pain patients: factors associated with increased risk. Pain 2004;111(1-2):201-208.

(80) Spallek J, Reeske A, Norredam M, Nielsen S, Lenhhardt J, Razum O. Suicide among immigrants in Europe - a systematic literature review. European Journal of Public Health 2014;25(1):63-71.

(81) Tenore P. Psychotherapeutic benefits of opioid agonist therapy. Journal of Addictive Diseases 2008;27(3):49-65.

(82) Tossani E. The concept of mental pain. Psychother Psychosom 2013;82(2):67-73.

(83) Troister T, Holden R. A two-year prospective study of psyache and its relationship to suicidality among high-risk undergraduates. 2012 Journal of Clinical Psychology;68(9):1019-1027.

(84) Troister T, Holden R. Comparing psychache, depression, and hopelessness in their associations with suicidality: A test of Shneidman's theory of suicide. Personality and Individual Differences 2010;Volume 49(Issue 7):689-693.

(85) Turecki G, Brent DA. Suicide and suicidal behaviour. Lancet 2016 Mar 19;387(10024):1227-1239.

(86) Wolrd Health Organization. Preventing suicide: A global imperative. 2014.

(87) Young E, Lariviere W, Belfer I. Genetic Basis of Pain Variability: Recent Advances. Journal of Medical Genetics 2012;49(1):1-9.

(88) Yovell Y, Bar G, Mashiah M, Baruch Y, Briskman I, Asherov J, et al. Ultra-Low-Dose Buprenorphine as a Time-Limited Treatment for Severe Suicidal Ideation: A Randomized Controlled Trial. American Journal of Psychiatry 2016;173(5):491-498.

. Journal Loss and Trauma 2011;16(5):402-402-412.

(53) Meerwijk E,L, Biro D. Toward a Unifying Definition of Psychological Pain; Is there such a thing as psychological pain? And why it matters. Cult Med Psychiatry 2010 Dec;16; 34(5; 4):402; 658-412; 667.

(54) Mills J, Green K, Reddon J. An evaluation of the Psychache Scale on an offender population. Suicide Life Threat Behav. 2005;35(5):570-580.

(55) Minzenberg M, Lesh T, Niendam T, Yoon J, Cheng Y, Rhoades R, et al. Frontal motor cortex activity during reactive control is associated with past suicidal behavior in recent-onset schizophrenia. Crisis 2015b;36:363-370.

(56) Minzenberg M, Lesh T, Niendam T, Yoon J, Cheng Y, Rhoades R, et al. Conflict-related anterior cingulate functional connectivity is associated with past suicidal ideation and behavior in recent-onset schizophrenia. Journal of Psychiatric Research 2015a;65:95-101.

(57) Minzenberg M, Lesh T, Niendam T, Yoon J, Cheng Y, Rhoades R, et al. Control-related frontal-striatal funciton is associated with past suicidal ideation and behavior in patients with recent-onset psychotic major mood disorders. Journal of Affective Disorders 2015c;188:202-209.

(58) Nock M, Park JM, Finn C, Deliberto T, Dour H, Banaji M. Measuring the suicidal mind: implicit cognition predicts suicidal behavior. Psychological science 2010;21(4):511-517.

(59) O'Connor R, Nock M. The psychology of suicidal behaviour. Lancet Psychiatry 2014;1.

(60) Olie E, Courtet P, Poulain V, Guillaume S, Ritchie K, Artero S. History of suicidal behaviour and analgesic use in community-dwelling elderly. Psychotherapy and Psychosomatics 2013;82(5):341-343.

(61) Orbach I, Mikulincer M, Sirota P, Gilboa-Schechtman E. Mental pain: a multidimensional operationalization and definition. Suicide Life Threat Behav 2003 Fall;33(3):219-230.

(62) Pachkowski MC, May AM, Tsai M, Klonsky ED. A Brief Measure of Unbearable Psychache. Suicide Life Threat Behav 2019 Dec;49(6):1721-1734.

(63) Panksepp J, Solms M. What is neuropsychoanalysis? Clinically relevant studies of the minded brain. Trends in Cognitive Sciences 2012;16(1):6-8.

(64) Patterson A, Holden R. Psychache and suicide ideation among men who are homeless: a test of Shneidman's model. Suicide and Life Threatening Behavior 2012;42(2):147-156.

(65) Patterson A,A, Holden R,R, Mee S, Bunney BG, Bunney WE, Hetrick W, et al. Psychache and Suicide Ideation among Men Who Are Homeless: A Test of Shneidmanâ€™s Model; Assessment of psychological pain in major depressive episodes. J Psychiatr Res 2011 Nov;42; 45(2; 11):1504-1510.

(66) Pereira EJ, Kroner DG, Holden RR, Flamenbaum R. Testing Shneidman's model of suicidality in incarcerated offenders and in undergraduates. Personality and Individual Differences 2010;49(8):912-917.

(67) Pompili M, Lester D, Leenaars AA, Tatarelli R, Girardi P. Psychache and suicide: a preliminary investigation. Suicide Life Threat Behav 2008 Feb;38(1):116-121.

(68) Richards B. Suicide and internalised relationships: A study from the perspective of psychotherapists working with suicidal patients. British Journal of Guidance & Counselling 1998;27(1):85-98.

(69) Rizvi SJ, Iskric A, Calati R, Courtet P. Psychological and physical pain as predictors of suicide risk: evidence from clinical and neuroimaging findings. Curr Opin Psychiatry 2017 Mar;30(2):159-167.

(70) Scarr E, Money T, Pavey G, Neo J, Dean B. Mu opioid receptor availability in people with psychiatric disorders who died by suicide: a case control study. BMC Psychiatry. 2012;12(126).

(71) Schutt R, Meschede T, Rierdan J. Distress, Suicidal Thoughts, and Social Support Among Homeless Adults*. Journal of Health and Social Behavior 1994;35(2):134-142.

(72) Shneidman ES. The suicidal mind. Oxford University Press 1996.

(73) Shneidman ES. Suicide as psyache. Journal of Nervous and Mental Disease 1993(181):147-149.

(74) Shneidman E. Perspectives on suicidology. Further reflections on suicide and psychache. Suicide Life Threat Behav. 2998;28(3):245-250.

(75) Shneidman ES. The psychological pain assessment scale. Suicide Life Threat Behav 1999 Winter;29(4):287-294.

(76) Shneidman ES. Suicide as psychache. J Nerv Ment Dis 1993 Mar;181(3):145-147.

(77) Shneidman ES. A possible classification of suicidal acts based on Murray's need system. Suicide Life Threat Behav 1980 Fall;10(3):175-181.

(78) Smith A, Ribeiro J, Mikolajewski A, Taylor J, Joiner T, Iacono W. An examination of environmental and genetic contributions to the determinants of suicidal behavior among male twins.
. Psychiatry Research 2012;197(1-2):60-65.

(79) Smith M, Edwards R, Robinson R, Dworkin R. Suicidal ideation, plans, and attempts in chronic pain patients: factors associated with increased risk. Pain 2004;111(1-2):201-208.

(80) Spallek J, Reeske A, Norredam M, Nielsen S, Lenhhardt J, Razum O. Suicide among immigrants in Europe - a systematic literature review. European Journal of Public Health 2014;25(1):63-71.

(81) Tenore P. Psychotherapeutic benefits of opioid agonist therapy. Journal of Addictive Diseases 2008;27(3):49-65.

(82) Tossani E. The concept of mental pain. Psychother Psychosom 2013;82(2):67-73.

(83) Troister T, Holden R. A two-year prospective study of psyache and its relationship to suicidality among high-risk undergraduates. 2012 Journal of Clinical Psychology;68(9):1019- 1027.

(84) Troister T, Holden R. Comparing psychache, depression, and hopelessness in their associations with suicidality: A test of Shneidman's theory of suicide. Personality and Individual Differences 2010;Volume 49(Issue 7):689-693.

(85) Turecki G, Brent DA. Suicide and suicidal behaviour. Lancet 2016 Mar 19;387(10024):1227-1239.

(86) Wolrd Health Organization. Preventing suicide: A global imperative. 2014.

(87) Young E, Lariviere W, Belfer I. Genetic Basis of Pain Variability: Recent Advances. Journal of Medical Genetics 2012;49(1):1-9.

(88) Yovell Y, Bar G, Mashiah M, Baruch Y, Briskman I, Asherov J, et al. Ultra-Low-Dose Buprenorphine as a Time-Limited Treatment for Severe Suicidal Ideation: A Randomized Controlled Trial. American Journal of Psychiatry 2016;173(5):491-498.